An adaptive patient-specific treatment approach for EGFR-driven stage IV lung cancer

Team Lung:
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Patient-specific treatment response
Using math modeling with patient-specific data, maximize days gained while avoiding toxicity.
Outline

- Strategy
- Signaling network model
- Optimization technique
- Feedback/Refinement
Less is more.

input -> tumor response model -> projected disease

signaling network model
druggable targets

escape routes

possible resistant nodes
synergism with MEK & PI3K inhibition

Jokinen et al, 2012
\[
\frac{dN_i(t, d)}{dt} = \left(\alpha_0 + \alpha_i^d - \beta_i^d\right) N_i + \sum_{i'} W_{i'i} N_{i'} + S_i^d M^r
\]

\[
i = n_1 n_2 n_3 n_4 n_5
\]

\[
d = d_1 d_2 d_3 d_4 d_5, \text{ where } d_i \in \{0, 1\}
\]

\[
M = \sum_{i'} N_{i'},
\]

\[
\alpha_i^d = \delta_{n21} \delta_{d20} \alpha_M + \delta_{n31} \delta_{d30} \alpha_H
\]

\[
\beta_i^d = \delta_{n10} \delta_{d11} \beta_E + \delta_{n21} \delta_{d21} \beta_{MET} + \delta_{n31} \delta_{d31} \beta_H + \delta_{d41} \beta_{MEK} + \delta_{n50} \delta_{d51} \beta_P^{(1)}
\]

\[
\quad + \delta_{n50} \delta_{d51} \delta_{n50} \delta_{d51} \left(\beta_{MEK} + \beta_P^{(1)}\right) + \delta_{n50} \delta_{n10} \delta_{d10} \delta_{n21} \delta_{d20} \delta_{n31} \delta_{d30} \beta_P^{(2)}
\]

\[
S_i^d = (1 + \eta_M \delta_{n21}) \delta_{d20}
\]

\[
\frac{d\Phi}{dt} = \varphi_m - \kappa \Phi
\]
response rates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>Value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_M$</td>
<td>growth from MET-overexpression</td>
<td>$\alpha_0/2$ day$^{-1}$</td>
<td>Navab et al. Neoplasia 2009 Based on $\alpha_M$</td>
</tr>
<tr>
<td>$\alpha_H$</td>
<td>growth from HER2-overexpression</td>
<td>$\alpha_0/2$ day$^{-1}$</td>
<td>Tomlinson et. al, PNAS, 1998</td>
</tr>
<tr>
<td>$\mu$</td>
<td>mutation rate</td>
<td>$10^{-7}$ day$^{-1}$</td>
<td>Navab et al. Neoplasia 2009</td>
</tr>
<tr>
<td>$\eta_M$</td>
<td>degree of MET-overexpression</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>$\gamma_M$</td>
<td>sensitivity to HGF</td>
<td>$10^{-2}$ cell$^{1/3}$day$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$s_{4,5}$</td>
<td>synergism between MEK &amp; PI3K</td>
<td>0.5</td>
<td>Jokinen et al., 2012 model specific</td>
</tr>
<tr>
<td>$\sigma_\beta$</td>
<td>std. of drug sensitivity</td>
<td>$\alpha_0/2$</td>
<td></td>
</tr>
<tr>
<td>$\kappa$</td>
<td>decay of toxicity</td>
<td>2.0</td>
<td>model specific</td>
</tr>
<tr>
<td>$\alpha_0$</td>
<td>baseline growth rate</td>
<td>0.2 log 2 day$^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\tau$</td>
<td>surface/volume ratio</td>
<td>2/3</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_E$</td>
<td>sensitivity to EGFR-inhibitor</td>
<td>0.53 day$^{-1}$</td>
<td>Rosell et al., 2012</td>
</tr>
<tr>
<td>$\beta_{MET}$</td>
<td>sensitivity to MET-inhibitor</td>
<td>0.18 day$^{-1}$</td>
<td>Landi et al., 2013</td>
</tr>
<tr>
<td>$\beta_H$</td>
<td>sensitivity to HER2-inhibitor</td>
<td>0.21 day$^{-1}$</td>
<td>Greve, J.D., 2012</td>
</tr>
<tr>
<td>$\beta_P$</td>
<td>sensitivity to PI3K-inhibitor</td>
<td>0.1 day$^{-1}$</td>
<td>Besse et al., 2011</td>
</tr>
<tr>
<td>$\beta_{MEK}$</td>
<td>sensitivity to MEK-inhibitor</td>
<td>0.038 day$^{-1}$</td>
<td>Jokinen et al., 2012</td>
</tr>
</tbody>
</table>

response rates

<table>
<thead>
<tr>
<th>Targeted gene</th>
<th>Drug</th>
<th>Clinical Benefit</th>
<th>$\beta$-value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Erlotinib</td>
<td>85-90%</td>
<td>0.53</td>
<td>Rosell et al., 2012</td>
</tr>
<tr>
<td>EGFR-T790M</td>
<td>Erlotinib</td>
<td>0%</td>
<td>0</td>
<td>Yang et al., 2012</td>
</tr>
<tr>
<td>MET-amp</td>
<td>MetMAb (+ erlotinib)</td>
<td>55%</td>
<td>0.18</td>
<td>Landi et al., 2013</td>
</tr>
<tr>
<td>HER2-amp</td>
<td>Afatinib</td>
<td>60-70%</td>
<td>0.21</td>
<td>Greve et al., 2012</td>
</tr>
<tr>
<td>PI3Kwt</td>
<td>GDC-0941</td>
<td>44%</td>
<td>0.1</td>
<td>Besse et al., 2011</td>
</tr>
</tbody>
</table>
VIRTUAL PATIENT COHORT: RESPONSE TO ERLOTINIB (SOC)
ERLOTINIB (SOC) CLONAL EVOLUTION

where 0=wt 1=mut
More is more.

Optimization technique: GA optimization

- Tumor response model
- Projected disease
- Choice of treatment schedule
possible patient timeline

Dx: EGFR+

6 weeks
12 weeks
18 weeks
24 weeks
30 weeks
36 weeks

weeks

3 yrs

erlotinib
erlotinib+metmab
erlotinib+metmab
break
metmab
selumetanib...

...
recombination

optimal Tx

50 days gained
\( \Phi > 1 \)

22 days gained
\( \Phi < 1 \)
SOC VS. GA-DERIVED TX SCHEDULE

SOC: erlotinib
GA: erlotinib+everolimus $\rightarrow$ metmab+everolimus $\rightarrow$ erlotinib+metmab $\rightarrow$ erlotinib+everolimus

$n=100$
p$<0.02$
FEEDBACK & REFINEMENT

Tx strategy response → new imaging biopsy → refined tumor response model → projected disease

GA optimization

initial conditions
new patient data

change in stromal component

serum HGF & biopsy

* death
GA finds optimal treatment schedule at Dx
Tumor burden

new patient information

imaging

biopsy
Update drug response

Tumor burden

* imaging

biopsy

Dx

6

12

18

24

30

36

weeks

3 yrs
New optimal Tx schedule

Tumor burden

Dx

imaging

weeks

3 yrs

6 12 18 24 30 36

break

...
new patient information

Tumor burden

Dx

6  12  18  24  30  36

imaging

biopsy

weeks

3 yrs
Update drug response

Tumor burden

Dx

6 12 18 24 30 36 weeks

3 yrs

imaging

biopsy
New optimal Tx schedule

Tumor burden

Dx

imaging

biopsy

weeks

break

3 yrs

and so on...
Conclusions

1) We have built a model that captures clonal dynamics of EGFR driven lung cancers.

2) Using a GA to optimize treatment scheduling of combinations of known drugs, the model predicts a treatment schedule that prolongs survival (45 days past that of standard of care).

3) Periodic updating and refinement of the model from patient-specific data should improve the model and the prediction of the treatment by the GA.
HYPOTHESIS: Pretreatment molecular phenotypes with real-time clinical variables obtained from plasma and imaging can be used to predict optimal drug sequence and thereby extend progression free survival.

**AIM 1:**
Refine the mathematical model using clinical data from a retrospective institutional cohort of advanced EGFR+ lung cancer patients.

**AIM 2:**
Utilize model-derived novel drug combination schedules and compare with standard of care using a metastatic EGFR driven *in vivo* model.
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